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MICROBIAL CELL FACTORIES

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# New challenges and opportunities for industrial biotechnology

Guo-Qiang Chen[1,2*]

**Abstract**

Industrial biotechnology has not developed as fast as expected due to some challenges including the emergences of alternative energy sources, especially shale gas, natural gas hydrate (or gas hydrate) and sand oil et al. The weaknesses of microbial or enzymatic processes compared with the chemical processing also make industrial biotech products less competitive with the chemical ones. However, many opportunities are still there if industrial biotech processes can be as similar as the chemical ones. Taking advantages of the molecular biology and synthetic biology methods as well as changing process patterns, we can develop bioprocesses as competitive as chemical ones, these including the minimized cells, open and continuous fermentation processes et al.

**Keywords:** Industrial biotechnology, Shale gas, Oil fields, PHB, Bioplastics, Biofuels, Bulk chemicals

The commercialization of industrial biotechnology is not as fast as we expected. Originally, we believe that production of bulk chemicals including biofuels, polymeric materials and chemical agents using microorganisms or enzymes will provide low cost, environmentally friendly products to partially replace petro-chemicals products [1]. However, this looks not so easy to materialize due to the facts that:

1. Petroleum does not rise in price too much after 2008 financial crisis, other alternative energy sources, especially shale gas, natural gas hydrate (or gas hydrate) and sand oil, have been discovered in large amount and their exploitations are increasingly moving toward a very competitive price;
2. The exhaustion of petroleum seems to be a remote reality
3. Agriculture raw materials for bioprocessing are becoming increasingly costly
4. Low cost raw material cellulose can not be easily used for microbial processes at least for the next 5–10 years
5. Bioprocessing is still not as effective as chemical processing, resulting in high cost of bio-products (Table 1)
6. Bioprocessing that requires large amount of fresh water has had increasing concerns in many water shortage areas
7. The chemical industry is also evolving competitive in various ways including environmentally friendliness, the use of renewable resources (biomass) for making chemicals that are normally derived from petro-chemicals
8. The rapid development of C1 chemical engineering products
9. Large amount of funding is not more directed to industrial biotechnology.

Taking the example of polyhydroxyalkanoates (PHA), a biopolyester family that has been exploited to become an industrial value chain [2-4], PHA has not been able to commercially produce in large scale due to the difficulty to lower the production cost especially for their applications as bioplastics that are considered as biodegradable and bio-based despite the possibility of using $CO_2$ as substrate [5].

To successfully commercialize PHA, we must keep working hard on the "high volume and low price" strategy by developing better PHA production strains and cost competitive processes. While for some special

Correspondence: chengq@mail.tsinghua.edu.cn
[1]MOE Key Lab of Bioinformatics and Systems Biology, Department of Biological Science and Biotechnology, School of Life Sciences, Tsinghua-Peking Center for Life Sciences, Tsinghua University, Beijing 100084, China
[2]Center for Nano and Micro Mechanics, Tsinghua University, Beijing 100084, China

**Table 1 Comparison of industrial biotechnology and chemical technology**

| Items | Industrial biotechnology | Chemical technology |
|---|---|---|
| Reaction Time | Slow: production takes days | Fast: production takes hours |
| Substrates | Agricultural products | Petroleum or its derivatives |
| Conversion of substrates to products | Low: e.g. PHB/glucose ≈ 33 wt% PHA/fatty acids ≈ 60 wt% | High: e.g. Polyethylene/ethylene ≈ 100% |
| Medium | Water | Mostly organic solvents |
| Consumption of water | A lot | Less |
| Reaction conditions | 30-40°C, normal pressure | Generally >100°C, High Pressures |
| Product concentration | Low: Several mg to 100 g/L | Very high |
| Product recovery cost | Very high | Low to medium |
| Processing | Normally discontinuous one | Can be continuous |
| Sterilization | Necessary | No need |
| Production facility cost | Very high | Low to high (explosive proof) |
| Waste water | Not toxic, easier to treat | Generally toxic, difficult to treat |

applications, "low volumes and high price" can be applied, such as products to be used for biomedical purposes, specialty polymers [6,7], chiral monomers, drug development and special applications et al. [8,9]. And this is generally true in order to survive this competitive environment for industrial biotechnology, it must be competitive with the chemical industry. Let's see what we can do to make this happen. In addition, it is also important to be able to develop processes that combined the advantages of chemical industry to supplement the weaknesses of industrial biotechnology (Table 1).

The newly emerging synthetic biology approaches may offer some clues for developing competitive technology for industrial biotechnology to produce "high volume and low price" products (Table 2). At the same time, bio-processing should try to become as similar as the chemical industry, including the need to develop continuous and open fermentation processes for e.g. making biofuels and PHA bioplastics [10-12]. Also, from now and toward a distant future, foods are still important for feeding the world population, the development of bioprocesses based on kitchen waste or activated sludge as substrates may also be an important option for a competitive industrial biotechnology (Table 2).

Combination of bio- and chemical processes can offer a lot of advantages including bio-based ($CO_2$ reduction) and fast reaction. Typical example includes the bioproduction of lactic acid from anaerobic fermentation

**Table 2 Problems to be solved for making industrial biotechnology competitive to chemical technology**

| Problems | Weakness of Industrial biotechnology | Possible solutions |
|---|---|---|
| Microorganisms grow too slow | Slow: production takes days | Minimizing the microbial cells |
| Microbes can not use mixed substrates | Agricultural products are mostly mixed substrates | Assembling pathways that can metabolize mixed substrates |
| Low conversion of substrates to products | Cell metabolism turn substrates into $CO_2$, $H_2O$ & byproducts | Removing unnecessary pathways consuming substrates |
| High Consumption on fresh $H_2O$ | Fresh $H_2O$ as medium et al. | Utilization of sea water for cell growth |
| Microbial cells grow to very low density | Product concentration low: Several mg to 100 g/L | Minimizing oxygen demand for aerobic cells & reducing Quorum sensing effects |
| Discontinuous processing | Contamination concerns | Developing continuous process |
| Sterilization costs high | High pressed steam | Contamination resisting strains grown in open systems |
| High energy demand for intensive aeration | Aerobic microorganisms need a lot of oxygen for growth | Developing anaerobic bioprocesses |
| Difficulty to control the bio-processes | Complicated cellular metabolisms | Artificial cells that contain only necessary metabolic pathways |
| One product by one microbial organism | Different organism has different strength. | Development of a platform organism for many products |
| Organisms consume food related products | Food for Fuels (Chemicals) | Kitchen wastes or activated sludge as substrates |
| Production facility costly | Costly materials and sensors | The use of carbon steel facilities et al. |

that is very effective and has only one single lactic acid product, and chemical polymerization of lactide to polylactide (PLA), a biodegradable green plastic [2,13]. The PLA story is a successful combination of bio- and chemical advantages. Others like succinic acid and 1,4-butanol bio-production and their copolymerization are under intensive R&D [2,13]. However, at the end, commercial successes have to be dependent on economy.

#### Competing interests

The author declares that he has no competing interests.

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